REMARKS/ ARGUMENTS

Applicant has carefully studied the final Examiner's Action mailed January 10, 2008, having a shortened statutory period for response set to expire April 10, 2008. The amendment appearing above and these explanatory remarks are believed to be fully responsive to the Action. Accordingly, this important patent application is now believed to be in condition for allowance.

Claim Rejections - 35 U.S.C. § 112

Office has rejected claims 1-5, 7, 17, and 20 under 35 U.S.C § 112, first paragraph, contending that the specification enables treatment of NSAIDS side effects, but does not enable preventing the side effects. The first paragraph of 35 U.S.C § 112 requires the specification describe the invention in sufficient detail to convey to one skilled in the art that the patentee possessed the claimed invention[1] and to describe how to use the invention such that an individual skilled in the art may use the invention without undue experimentation.[2] To determine whether a disclosure requires undue experimentation, a series of factors have been established, including the breadth of claims, nature of the invention, state of prior art, relative skill in the art, predictability in the art, the amount of direction or guidance, presence of working examples, and amount of experimentation needed.[3] The level of guidance is dictated by the amount of knowledge associated with the art and predictability of the art,[4] however an invention does not need to be completely tested to satisfy the enablement requirement.[5] 35 U.S.C. § 112 is satisfied if "the specification contains within it *a connotation* of how to use" the invention or the use is known in the art.[6] A specification does not require working examples, but may utilize prophetic examples to describe the invention based on "predicted results."[7] Further, the specification does not need an example if the invention may be used without undue experimentation.[8]

Breadth of Claims

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[1] *Lizardtech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1345, 76 U.S.P.Q.2d 1724 (Fed. Cir. 2005).
[2] MPEP 2164. MPEP 2164.01, citing *In re Wands*, 858 F.2d 731(Fed. Cir. 1988).
[3] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).
[4] MPEP 2164.03.
[5] *In re Wands*, 858 F.2d at 739. Finding that antibody-producing hybridomas did not need to be fully characterized, even though only 2.8 percent of cells deposited, in support of the patent, fell within the claims.
[6] MPEP 2164.01(c). (Emphasis added).
[7] MPEP 2164.02. Citing *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987).
[8] MPEP 2164.02.

In determining the breadth of the claims, the claim must be considered as a whole to determine whether the invention as claimed may be practiced without undue experimentation.[9] Provided "the specification disclosed *at least* one method for making and using the claimed invention" that correlates to the scope of the invention, the invention is enabled, [10] not everything necessary to practice the invention need be disclosed. [11]

Office states that the claims cover the prevention of side effects for anti-inflammatory drugs, which have "potentially many different presentations."[12] Further, non-steroidal anti-inflammatory drugs (NSAIDs) have numerous side effects, from minor irritations to serious complications,[13] which differ from steroidal anti-inflammatory drugs (SAIDs)[14]. Office concludes by stating the invention may or may not address all the side effects.

Applicant concurs with Office, only in that the invention addresses a wide array of side effects. Claim 1 provides for "preventing, reducing and reversing the toxic effects of anti-inflammatory drugs[.]" Claim 1 does not require all toxic side effects be prevented, reduced or reversed, but requires prevention or treatment of at least one side effect of the drugs. To prevent, reduce, and reverse the toxic effects of an anti-inflammatory drug, the invention must keep a toxic effect from happening[15], diminish the extent of a toxic effect[16], and "undo or negate" a toxic effect[17] of an anti-inflammatory drug.

NSAID effects are generally mediated through cyclooxygenase (COX) enzyme inhibition.[18] The inhibition of COX causes reduced eicosanoid synthesis.[19] Nonselective COX inhibition causes adverse effects, including gastrointestinal (GI) problems like gastroduodenal ulcers and gastrointestinal bleeding.[20] Use of selective COX-2 inhibitors has been shown to

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[9] MPEP2164.08.
[10] MPEP 2164.01(b). (Emphasis added).
[11] MPEP2164.08
[12] Paragraph A, page 4 of the non-final Office Action, dated January 11, 2008.
[13] *Id.*
[14] *Id.* at page 5.
[15] to keep from happening or existing- http://www.merriam-webster.com/dictionary/preventing
[16] to diminish in size, amount, extent, or number- http://www.merriam-webster.com/dictionary/reducing
[17] to undo or negate the effect of (as a condition or surgical operation)- http://www.merriam-webster.com/dictionary/reversing
[18] Page 2 of the Application. J. Masferrer, K. Seibert, B. Zweifel, P. Needleman, "Endogenous Glucocorticoids Regulate an Inducible Cyclooxygenase Enzyme," Proc. Nat. Acad. Sci., 1992, 89, 3917-3921, page 3919, column 2.
[19] *Id.*
[20] Unknown author, "Balancing Cardiovascular Rishs and Gastrointestinal Outcomes in NSAID Users; A Report from a Symposium held During the American College of Gastroenterology 71st Annual Meeting and Postgraduate Course," Gastroent. & Hepat., Mar. 2007, 3:3, 4-13, page 4, column 1.

alleviate GI side effects, but increases adverse cardiovascular events.[21] Like NSAIDs, SAIDs has been shown to also reduce inflammatory response through COX inhibition and eicosanoid formation inhibition.[22] The anti-inflammatory effects of NSAIDs and SAIDs rely on the same pathway, at least partly, and therefore the side effects of both NSAIDs and SAIDs may be prevented and treated by targeting such common pathways between the NSAIDs and SAIDs.

The specification shows pretreating with a MAO-B inhibitor, L-deprenyl, before administering a NSAID provided protection to gastrointestinal mucous after one pretreatment and reverses gastrointestinal lesions by one week pretreatment.[23] Rats were provided with MAO inhibitor (L-deprenyl or propargylamine) or a solvent negative control.[24] One hour later, NSAID was administered to the rat.[25] After 8 hours, NSIAD treatment produced gastric lesions.[26] However, pretreatment with L-deprenyl or propargylamine prevented formation of gastric lesions.[27] In similar experiments conducted over 7 days, pretreatment with L-deprenyl or propargylamine prevented formation of gastric lesions and reversed lesions.[28]

The application also discloses MAO inhibitor tests on C-reactive protein, which is elevated in obesity and diabetes and a possible side effect of hormone therapy.[29] Blood samples were taken from human subjects, followed by administration of L-deprenyl.[30] After seven days, blood CRP levels were reduced 30% in L-deprenyl-treated individuals.[31]

Not every embodiment or procedure to practice the invention need be disclosed for the invention to be enabled.[32] The application discloses that MAO inhibitors L-deprenyl and propargylamine effectively prevent formation of gastric lesions and reverse lesion progression during prolonged treatment, as seen in table 3.[33] The claims do not require all side effects of each drug be prevented, but rather for enablement the invention must prevent or treat at least one

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[21] *Id.* at page 4, column 2; page 6, column 2.
[22] J. Masferrer, K. Seibert, B. Zweifel, P. Needleman, "Endogenous Glucocorticoids Regulate an Inducible Cyclooxygenase Enzyme," Proc. Nat. Acad. Sci., 1992, 89, 3917-3921, page 3917, columns 1-2; page 3919, column 2; page 3920, columns 1-2.
[23] Example 5, pages 22-23; table 3, page 25 of the Application.
[24] Page 22 of the Application.
[25] *Id.*
[26] *Id.*
[27] *Id.* at page 23; table 3.
[28] *Id.*
[29] *Id.* at page 24.
[30] *Id.*
[31] *Id.*
[32] MPEP2164.08
[33] *Id.* at page 23; table 3.

side effect of the drugs. L-deprenyl and propargylamine treatment is shown effective in preventing and reducing NSAID side effects. SAIDs act through the same pathway as NSAIDs, by inhibiting COX, to produce an anti-inflammatory effect. Though NSAIDs and SAIDs have different side effects, both anti-inflammatory treatments utilize COX-dependent pathways. As such, the application discloses at least one example of preventing the side effects of NSAIDs and SAIDs. Therefore, NSAIDs and SAIDs may be effectively treated by compounds that target such similar pathways and the claims are consistent with the scope of the disclosure.

Nature of the Invention

Office states the claims are drawn to preventing, reducing, and reversing the toxic side effects of anti-inflammatory drugs and enhancing beneficial effects of such drugs, and therefore the invention is extremely complex.[34] As stated *supra*, the claimed invention requires an MAO inhibitor to prevent, reduce or reverse at least one side effect of an anti-inflammatory drug. Preventative and reductive treatments for anti-inflammatory drugs, such as synthetic prostagladins, proton pump inhibitors (PPI)[35], and vitamin C[36], have been tested for effectiveness in treating and preventing anti-inflammatory side effects. Therefore, the nature of the invention, while complex, is not outside the understanding of one skilled in the art.

State of the Prior Art

Office noted the state of the prior art is "relatively high" for treating side effects of anti-inflammatory drugs, but is underdeveloped for preventing side effects. The medicinal arts have developed some preventative and reductive treatments for anti-inflammatory drugs, such as synthetic prostagladins, proton pump inhibitors (PPI)[37], and vitamin C[38]. Co-administering NSAIDs with proton pump inhibitors (PPI)[39] or vitamin C[40] has shown to effectively limit GI toxicity damage. While PPIs are the preferred co-treatment, vitamin C has free radical

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[34] Page 5 of the non-final Office Action, dated January 11, 2008.
[35] D. Graham, et al., "Ulcer Prevention in Long-Term Users of Nonsteroidal Anti-inflammatory Drugs," Arch. Intern. Med., Jan. 28, 2002; 162: 196-175, pages 169, 173-174.
[36] J. Becker, W. Domschke, T. Pohle, "Current Approaches to Prevent NSAID-Induced Gastropathy- COX Selectivity and Beyond," Br. J. Pharmacol., Dec. 2004; 58(6):587-600, abstract.
[37] D. Graham, et al., "Ulcer Prevention in Long-Term Users of Nonsteroidal Anti-inflammatory Drugs," Arch. Intern. Med., Jan. 28, 2002; 162: 196-175, pages 169, 173-174.
[38] J. Becker, W. Domschke, T. Pohle, "Current Approaches to Prevent NSAID-Induced Gastropathy- COX Selectivity and Beyond," Br. J. Pharmacol., Dec. 2004; 58(6):587-600, abstract.
[39] A. Lanas, R. Hunt, "Prevention of Anti-Inflammatory Drug-Induced Gstrointestinal Damage: Benefits and Risks of Therapeutic Strategies," Ann. Med. 2006; 38(6):415-428, abstract.
[40] J.C. Becker, W. Domschke, T. Pohle, "Current Approaches to Prevent NSIAD-Induced Gastropathy-COX Selectivity and Beyond," Br. J. Clin. Pharmacol., Dec. 2004; 58(6):587-600, abstract.

scavenging, and the ability to induce haeme-oxygenase I in gastric cells, an antioxidant and vasodilative enzyme.[41]

Many of these drugs target specific events caused by anti-inflammatory drugs, such as inhibiting gastrointestinal acid pumps act as antagonists to ulceration, and have been effectively used to both treat[42] and prevent[43] gastrointestinal events. Drug interactions have also been analyzed for some concurrently used drugs, such as disease-modifying anti-rheumatic drugs (DMARDs)[44]. The specification provides examples of MAO inhibitors preventing anti-inflammatory drug side effect damage, as discussed *supra*. The state of the art does provide information on preventing anti-inflammatory drug side effects. While the prior art does not teach compounds similar to the present invention prevent side effects of anti-inflammatory drugs, the specification itself does have illustrative examples of such prevention. Further, Office contends the compound must "prevent all of the above possible side effects of anti-inflammatories."[45] However, claim 1 requires "preventing, reducing and reversing the toxic effects of anti-inflammatory drugs[,]"[46] but does not require preventing, reducing, or reversing all toxic effects of the drugs. Preventing the formation of one toxic side effect of an anti-inflammatory drug is preventing the toxic effect of an anti-inflammatory drug. As such, the specification and prior art support claim 1.

Relative Skill in the Art

Office states that the level of ordinary skill in the art is "that of a physician."[47] The level of skill in the art is determined by determining the subject matter at the time of filing.[48] The current invention is classified as "Art Unit" 1614, comprising drugs and "bio-affecting" compositions.[49] The pharmaceutical, medicinal, and scientific arts are considered highly skilled

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[41] *Id.*

[42] J.C. Becker, et al., abstract ("Proton pump inhibitors are the comedication of choice as they effectively reduce gastrointestinal adverse events[.]").

[43] A. Lanas, R. Hunt, "Prevention of Anti-Inflammatory Drug-Induced Gastrointestinal Damage: Benefits and Rsiks of Therapeutic Strategies," Ann. Med., 2006; 38(6):415-428, abstract ("Those at risk [for GI side effects] should be considered for *prevention* with misoprostol, proton pump inhibitor (PPI) or COX-2 selective inhibitor[.]").

[44] H. Yajima, J. Yamao, H. Fukui, Y. Takakura, "Up-to-Date Information on Gastric Mucosal Lesions from Long-Term NSAID Therapy in Orthopedic Outpatients: A Study Using Logistic Regression Analysis," J. Orthop. Sci., 2007; 12: 341-346, page 342. (DMARDs listed include bucilamine and methotrexate).

[45] Paragraph C, pages 5-6 of the non-final Office Action, dated Jan. 10, 2008.

[46] See, claim 1, page 30 of the Application.

[47] Paragraph D, page 6 of the non-final Office Action, dated Jan. 10, 2008.

[48] MPEP 2164.05(b).

[49] http://www.uspto.gov/web/offices/opc/caau/1614_1754.htm, Definitions of art units.

arts. As such, the specification does not need to specify limitations if the prior art or knowledge of similar physiological or biological activity in the biotech and medical sciences.[50]

Predictability in the Art

Office contends the lack of guidance from the specification and prior art with regards to preventing side effects make the invention unpredictable. Other work in the field has shown the side effects of anti-inflammatory drugs may be prevented through co-administration of other compounds.[51,52] However, until the current invention, prevention relied on addressing biological activities of specific side effects. The examples provided in the specifications show the effectiveness of L-deprenyl and propargylamine pretreatment in preventing formation of gastric lesions after acute treatment,[53] and prevented formation of gastric lesions and reversed lesions after continued treatment.[54] Therefore, any questions as to the predictability of the invention have been addressed by the specification and work in the field.

Amount of Direction or Guidance

The specification does not need an example if the invention may be used without undue experimentation.[55] The medicinal and scientific arts are highly skilled arts, as discussed *supra*. The specification provides guidance as to the timing and amount of MAO inhibitor to use to effectively prevent anti-inflammatory side effects.[56] For example, L-deprenyl shows a reduction in gastric lesion damage at 100 mg/kg and at 200 mg/kg; 21-40% and 1-20% of lesions in mice treated only with anti-inflammatory, respectively.[57] The specification also includes working examples of the invention in reducing gastric ulceration, illustrating that the administration of MAO inhibitor provides a protective effect for cells.[58] Therefore, the specification provides both direction and guidance as to the timing and dosage of MAO inhibitor to use to effectively prevent anti-inflammatory side effects.

Presence of Working Examples

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[50] MPEP 2164.01(c).
[51] D. Graham, et al., "Ulcer Prevention in Long-Term Users of Nonsteroidal Anti-inflammatory Drugs," Arch. Intern. Med., Jan. 28, 2002; 162: 196-175, pages 169, 173-174.
[52] J. Becker, W. Domschke, T. Pohle, "Current Approaches to Prevent NSAID-Induced Gastropathy- COX Selectivity and Beyond," Br. J. Pharmacol., Dec. 2004; 58(6):587-600, abstract.
[53] *Id.* at page 23; table 3.
[54] *Id.*
[55] MPEP 2164.02.
[56] Pages 22-23; 25, table 3 of the Application.
[57] Page 25, table 3 of the Application.

A specification does not require working examples, but may utilize prophetic examples to describe the invention based on "predicted results."[59] The specification does include working examples of the invention in reducing platelet activation and reducing gastric ulceration.[60] Cardiovascular events, caused by anti-inflammatory treatment, develop due to the prothrombic activity of the drugs, causing platelet coagulation and resulting in cardiovascular events like congestive heart failure, stroke, vascular death, and myocardial infarction.[61] Leukocyte activation and adhesion is known in the art,[62] and pretreatment of L-deprenyl (5 mg/kg) inhibited leukocyte activation induced by TNF-α,[63] thereby preventing cardiovascular events caused by anti-inflammatory drugs. Additionally, the specification discloses L-deprenyl and propargylamine reduces and prevents gastric lesions,[64] commonly caused by anti-inflammatory drug treatment. Thus, the specification illustrates that the treatment of an MAO inhibitor effectively prevents, reduces, and reverses the effects of anti-inflammatory drugs.

Amount of Experimentation Needed

Office states a skilled artisan must envision a combination of pharmaceutical carrier, dosage, duration of treatment, rout of administration, and determine an animal model before the invention may be practiced.[65] The specification and provides the MAO inhibitor may be administered numerous ways, including orally, parentally, intravenously, intraduodenally, intracutaneously, and intranasally.[66] The specification also teaches a method of chemically linking an MAO inhibitor to a NSAID[67] and teaches an unlinked MAO inhibitor may administered prior to anti-inflammatory drug treatment.[68]

The specification provides the NSAID may be administered in an effective amount, as determined by standard procedures evidenced by the Physician's Desk Reference (PDR),[69] and

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[58] Page 25, table 3 of the Application (Providing lesion reduction at provided dosages for L-deprenyl and propargyline).
[59] MPEP 2164.02. Citing *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987).
[60] Examples 3 and 5, pages 21-23 of the Application.
[61] *Id.* at page 5-6.
[62] See, T. Thomas, J. Rhodin, L. Clark, A. Garces, "Progestin Initiate Adverse Events of Menopausal Estrogen Therapy," Climacteric, Dec. 2003; 6(4):293-301.
[63] Example 3, page 21 of the Application.
[64] Example 5, page 23; table 3, page 25 of the Application.
[65] Paragraph H, page 6 of the non-final Office Action, dated Jan. 10, 2008.
[66] Page 19 of the Application.
[67] Example 1, pages 20-21 of the Application.
[68] Example 5, pages 22-23 of the Application.
[69] Page 18 of the Application.

usually between 3 and 40 mg/kg body weight for NSAIDs.[70] The MAO inhibitor may be administered in amounts at 0.1 to 10 times the molar amount of NSAID, and may be extrapolated from the PDR.[71] The MAO inhibitor is shown to effectively reduce, prevent, and reverse anti-inflammatory drug treatment at 100 mg/kg to 200 mg/kg for L-deprenyl and 250 mg/kg for propargylamine.[72]

"Enablement is not precluded by the necessity for some experimentation *such as routine screening*."[73] Varying the timing for treatment administration and/or the dosage of anti-inflammatory and MAO inhibitor is essentially a drug screening process. According to *Wands*, screening is within the routine practice of the medicinal and scientific arts.[74] Based on the prior work performed in the art, the level of skill in the art, and the disclosure, the invention is adequately described for prevention, reduction, and reversion of the side effects of anti-inflammatory drugs.

35 U.S.C. § 112 is satisfied if "the specification contains within it *a connotation* of how to use" the invention or the use is known in the art.[75] Office bears the initial burden to show the specification does not enable the claimed invention. The medicinal and scientific arts are highly skilled arts, as discussed *supra*. The specification provides guidance as to the timing and dosage of MAO inhibitor, as refers to the prior art (PDR) for calculations on patient dosages. The specification does include working examples of the invention in gastrointestinal ulceration prevention and reduction/ reversion, as well as prevention of cardiovascular events. As such, based on the prior art, skill of the ordinary artisan, and disclosure, the invention is adequately described to allow a skilled artisan to use the invention for treatment for preventing, reducing and reversing the toxic effects of anti-inflammatory drugs. The *Wands* factors indicate the invention may be performed without undue experimentation, as discussed *supra*. Accordingly, it is respectfully requested that the objection to the specification be withdrawn by the Office.

Claim Rejections - 35 U.S.C. § 103

[70] Page 19 of the Application.
[71] *Id.*
[72] See, table 3, page 25 of the application.
[73] *In re Wands*, 858 F.2d at 736-737. (Emphasis added).
[74] See generally, *In re Wands*, 858 F.2d at 739.
[75] MPEP 2164.01(c). (Emphasis added).

To support a rejection under 35 USC §103(a), a *prima facie* case of obviousness must be made[76]. To establish a *prima facie* case, the art must provide a reasonable expectation of success[77] and every word in a claim limitation must be considered.[78] The claimed invention must be considered as a whole for obviousness.[79] Further, the prior art must be reviewed as a whole, including parts that teach away from the invention.[80] References cannot be combined if a reference teaches away from the combination.[81] Finally, even though all aspects of the invention are taught, the invention is not *per se* obvious.[82]

Applicant acknowledges the Office has rejected claims 1-5, 7, 17 and 20 under 35 U.S.C. 103(a) as being unpatentable over Glavin, et al. (Neurosci. Ltrs., 1986) and Lianping, et al.[83]

Office states Glavin teaches an association between duodenal ulcer occurrence and dopamine deficiency,[84] and administration of MAO-B inhibitor L-deprenyl prevented ulcers in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated dopamine-deficient rats.[85] Office then contends Lianping teaches MAO inhibitors inhibit gastrin release, protecting mucosa from ulceration.[86]

Applicant agrees with Examiner, in that Glavin teaches that duodenal ulcers formation is correlated with dopamine, such that depleting dopamine with MPTP induces duodenal ulceration.[87] Further, Glavin teaches treatment with pargyline or L-deprenyl reduces stress-induced ulceration.[88] This result is apparently attributable to dopamine, and dopamine function within the brain is "an essential component of resistance to stress ulcerogenesis."[89]

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[76] MPEP 2143.
[77] MPEP 2143.02.
[78] MPEP 2143.03.
[79] MPEP 2141.02(I).
[80] MPEP 2141.02, 2141.02(VI).
[81] MPEP 2145(X)(D)(2).
[82] See, MPEP 2143.01(IV).
[83] Page 11 of the non-final Office Action, dated Jan. 10, 2008.
[84] *Id.*
[85] *Id.* at page 12.
[86] *Id.*
[87] G. Glavin, A. Dugani, C. Pinsky, "L-Deprenyl Attenuates Stress Ulcer Formation in Rats," Neurosci. Ltrs. 1986; 70:379-381, page 380.
[88] *Id.* at pages 380-381.
[89] *Id.* at page 381.

Lianping teaches that elevated levels of central nervous system dopamine or norepinephrine lower gastric output and limits gastrointestinal mucosal injury.[90] L-deprenyl pretreatment attenuates dopamine depletion[91], increasing dopamine and reducing gastric acid output and ulceration[92]. However, Lianping expressly limits its teachings to determining protection via antisecretory effects of MAO-B inhibition.[93]

The present invention provides a MAO inhibitor treatment to limit damage and side effects caused by NSAIDs and SAIDs, not stress induced ulceration. Lianping and Glavin fail to teach the current invention, which, as described and claimed, applies to "preventing, reducing and reversing the toxic effects of anti-inflammatory drugs[.]"[94] Anti-inflammatory drugs typically work through mediating the production of prostanoids, which is generally accomplished through COX inhibition and eicosanoid inhibition.[95, 96, 97] The administration of MAO inhibitors has numerous localized effects, including preventing apoptosis, inhibiting oxidative stress, stimulating expression and activity of antioxidant enzymes, stimulating nitric oxide synthase, and inhibiting platelet activation and thrombic activity,[98] which act to prevent, reduce, and reverse the effects of anti-inflammatory drugs. Therefore, the combination of Lainping and Glavin fail to obviate the present invention.

Further, Lainping fails to obviate the current invention as the current invention does not rely on dopamine functions to modulate the side effects of anti-inflammatory drugs, but rather relies on the antioxidant, free radical scavenging, properties of MAO inhibitors.[99] The invention also relies on the ability of MAO inhibitors to prevent apoptosis, inhibit oxidative stress, stimulate expression and activity of antioxidant enzymes, stimulate nitric oxide synthase, and inhibit platelet activation and thrombic activity.[100] Lianping expressly limited its teachings to the antisecretory effects of MAO-B inhibition, and therefore does not teach the current invention.

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[90] Lianping Xing, J. Seaton, G. Kauffman, "Monoamine Oxidase B Inhibition Reduces Gastric Mucosal Blood Flow, Basal Acid Secretion, and Cold Water Restrain-Induced Gastric Mucosal Injury in Rats," Digestive Dis. And Sci., Jan. 1990; 35(1):61-65, page 64, column 1; page 63, table 3.
[91] *Id.* at page 63, column 2.
[92] *Id.* at page 63, column 1.
[93] *Id.* at page 64, column 1 ("These studies were not designed to determine whether protection of the gastric mucosa is related to any effect of the MAO-B inhibitor other than the antisecretory effect.").
[94] Page 30, claim 1 of the Application.
[95] Page 2 of the Application. J. Masferrer, et al., page 3919, column 2.
[96] *Id.*
[97] J. Masferrer, et al., page 3917, columns 1-2; page 3919, column 2; page 3920, columns 1-2.
[98] *Id.*
[99] Page 17 of the Application.

Glavin teaches the effects of dopamine levels may control gastric acid output and ulceration. However, neither reference teaches the localized effect of MAO inhibitors, specifically prevention of cellular damage due to COX inhibition and anti-inflammatory drug treatment. The current invention uses MAO inhibitors to provide localized effects against apoptosis and oxidative stress, and localized stimulatory effects on expression and activity of antioxidant enzymes, and nitric oxide synthase,[101] which act to prevent, reduce, and reverse the effects of anti-inflammatory drugs independent of dopamine levels.

Applicant traverses the finding that treatment of MPTP, known to cause mucosal injury through dopamine reduction, and stress induced ulceration would make the present invention, using MAO inhibitors to prevent toxic side effects of anti-inflammatory agents, obvious. The present invention does not treat stress-induced mucosal injury, per se, and does not solely claim or describe mucosal injury prevention. Rather, the invention teaches modulation of the side effects of anti-inflammatory drugs, which includes modulating the prothrombic activity of anti-inflammatory drugs, which the references do not discuss. The claimed invention is limited to preventing, reducing and reversing the toxic side effects of anti-inflammatory drugs through MAO inhibitor administration. The references fail to address the toxic effects of anti-inflammatory drugs, and fail to teach a method for preventing, reducing or reversing the side effects, which include more than solely mucosal injury.

As such, Applicant respectfully requested that the rejection of claims 1-5, 7, 17 and 20 be withdrawn

Conclusion

Applicant respectfully requests that a timely Notice of Allowance be issued in this case. If the Office is not fully persuaded as to the merits of Applicant's position, or if an Examiner's Amendment would place the pending claims in condition for allowance, a telephone call to the undersigned at (813) 925-8505 is requested.

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[100] *Id.*
[101] *Id.*

Very respectfully,

SMITH & HOPEN

By:_____

Dated: April 7, 2008
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CERTIFICATE OF ELECTRONIC TRANSMISSION

(37 C.F.R. 2.190 (b))

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/lauren reeves/

Date: April 7, 2008

Lauren Reeves